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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/425,633	10/22/99	CHEE	M A-68087-1/RM

HM12/0502

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EXAMINER

FORMAN, B

ART UNIT	PAPER NUMBER
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1655

13

DATE MAILED: 05/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/425,633

Applicant(s)

CHEE ET AL.

Examiner

BJ Forman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 February 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17-41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8, 9, 12, 13
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____

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DETAILED ACTION

1. This action is in response to papers filed 28 February 2001 in Paper No. 11 in which claims 1-16 were canceled and new claims 17-41 were added. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action of Paper No.7 dated 25 August 2000 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 103 (a) as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,679,524), Walt et al. (U.S. Patent No. 6,023,540) and Lyamichev et al. (Nature Biotechnology, March 1999, 17: 292-296) are maintained and applied to the new claims based on Examiner's best understanding of the new claims. Applicant states that support for all new claims is found in the original claims (page 9-14 of the Response to Office Action). Therefore as far as the new claims can be understood, the previous rejection is maintained and applied to the new claims.

All of the arguments have been thoroughly reviewed and discussed below.

Currently claims 17-41 are under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 17-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are replete with confusing and contradicting recitations such that the scope of the new claims and how they may differ from the scope of the canceled claims is unclear. A few examples of the confusing and contradicting recitations are presented below.

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a. Claims 17-31 are indefinite in Claim 17 as being drawn to a method but the claim does not recite method steps which lead to “detecting”. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6. It is suggested that Claims 17 be amended to recite positive and active method steps e.g. hybridizing, attaching, and labeling.

b. Claims 17-31 are indefinite in Claim 17 for the recitation “a first label specific to said first nucleotide at said detection position” because “specific to” is a relational term but it is unclear whether the “label” relates to the “first nucleotide” and/or “detection position”. It is suggested that Claim 17 be amended to define the relationships.

c. Claims 17-31 are indefinite in Claim 17 a) in the recitation “hybridization complex” because only a target sequence is recited and therefore it is unclear whether the label is on the target sequence or another member of a complex. It is suggested that Claim 17 be amended to recite positive and active method steps for providing the hybridization complex e.g. hybridizing, ligating, capturing etc.

d. Claims 19-31 are indefinite in Claim 19 because the claim appears to be a method for making a first target sequence (step c) but the relationship between the first target sequence and the second target sequence is not evident.

e. Claim 20 & 28-31 are indefinite in Claim 20 because it is unclear how “said first label” relates to the first target sequence recited in Claim 17, i). It is suggested that the claim be amended to clarify.

f. Claims 21-31 are indefinite in Claim 21 b) and c) in the recitations “said detection position” because it is unclear whether the “detection position” being referred to is the

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“detection position” on the “first target sequence” recited in Claim 17, 1) or “second target sequence” as recited in Claim 21, a).

g. Claims 21-31 are indefinite in Claim 21 because the claim appears to be a method for making a first target sequence (step c) but the relationship between the first target sequence and the second target sequence is not evident.

h. Claim 22-26 are indefinite in Claim 22 for the recitation “said first and second dNTPs comprise first and second labels” because it is unclear whether and/or how the “first label” relates to the “first label” of Claim 17, 2).

i. Claims 23-26 are indefinite in the recitations “said first label” because it is unclear whether the label being referred to is the “first label” which is part of the “first target sequence” of Claim 17 or a first labeled dNTP of Claim 22.

j. Claim 32-37 are indefinite in Claims 32-34, b) because the steps appear to be method steps of hybridization and labeling, but the relationship between the “composition” and “altered probe” comprising a label is unclear. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6. It is suggested that the claims be amended to recite positive and active method steps e.g. hybridizing, ligating, digesting, labeling, and immobilizing.

k. Claim 38 is indefinite in the recitation of step b) because “the readout position” lacks proper antecedent basis in the claim and therefore it is unclear how the detected signal identifies the “detection position”. It is suggested that the claim be amended to provide proper antecedent basis and to clarify.

l. Claim 39 is indefinite in step a) because it is unclear how the “hybridization complex is formed” because the relationship between the capture probe and the target sequence and

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extension primer hybridized to the target sequence is not defined. Additionally, it is unclear how "contacting said microsphere...." recited in step b) extends the extension primer.

m. Claim 40 is indefinite in the recitation "forming an assay complex" because it is unclear what method steps are performed in the claimed "assay". It is suggested that the claim be amended to clarify.

n. Claim 41 is indefinite in the recitation "forming an assay complex" because it is unclear what method steps are performed in the claimed "assay". It is suggested that the claim be amended to clarify.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 17-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,679,524, filed 9 August 1996), Walt et al. (U.S. Patent No. 6,023,540) and Lyamichev et al. (Nature Biotechnology, March 1999, 17: 292-296) for reasons of record in the previous Office Action, mailed 24 August 2000 as applied to new claims 17-41 according to Examiner's best understanding of the claims.

Response to Arguments

6. Applicant argues that Nikiforov et al. and Walt et al. do not teach, suggest or provide motivation to modify or combine the references. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Nikiforov et al. teach a method comprising: providing a hybridization complex comprising a target sequence, a first oligonucleotide and a second oligonucleotide, adding a composition comprising a polymerase, a ligase and NTP

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mixture to allow the incorporation of the NTP to detect and identify the nucleotide at a detection position wherein the first oligonucleotide is attached to a microsphere (Columns 6-7 and Column 11, line 6-8) wherein the method comprises a plurality of detection probes (Example 1, Column 16, line 55-Column 17, line 1) and wherein the label comprises a functional group for addition of a fluorophore (see Albarella et al. Column 13, lines 41-50). While Nikiforov et al. do not teach the microsphere is on a surface and they do not teach each NTP comprise a unique fluorophore, Walt et al. teach the similar method wherein the microsphere is on a surface and each detection comprises a unique fluorophore (Column 4, lines 4-14) and they teach the motivation to modify the microsphere of Nikiforov et al. i.e. detecting and analyzing a numerous sequences rapidly and automatically using commercially available software (Column 4, lines 20-28). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the microsphere of Nikiforov et al. by positioning the microsphere on a surface wherein each detection position is identified by a unique fluorophore for the expected benefits specifically taught by Walt et al. i.e. detecting and analyzing a numerous sequences rapidly and automatically using commercially available software (Column 4, lines 20-28).

Applicant further argues that Nikiforov et al. do not teach single base extension, structure-specific enzymes or competitive hybridization. This argument is not found persuasive because Nikiforov et al. do teach single base extension (Column 6, lines 50-64) wherein the extra steps of Nikiforov et al. are encompassed by the open claim language "comprising" of the instant claims. Additionally, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., structure-specific enzymes and competitive hybridization) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant further argues that the examiner does not provide adequate motivation to modify the fluorescently detectable NTPs of Nikiforov et al. with each NTP comprising a unique fluorophore. The argument is not found persuasive because as stated in the previous action, the NTPs each having a unique fluorophore was well known in the art at the time the claimed invention was made. Specifically, Smith et al. (Nature, 1986, 321: 674-679) the uniquely labeled NTPs permit non-isotopic detection and identification of nucleotides using computerized automation (page 678, left column, last paragraph-right column first paragraph). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the labeled NTP of Nikiforov et al. by providing NTPs each having

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a unique fluorophore for the expected benefit of non-isotopic detection and identification of nucleotides using computerized automation as taught by Smith et al. (page 678, left column, last paragraph-right column first paragraph).

Applicant further argues that the examiner does not provide support for the motivation to modify the hatpens of Nikiforov et al. to provide the claimed haptens. This argument is not found persuasive because Nikiforov et al. teach hapten labels e.g. biotin and other suitable labels well know in the art (Column 13, lines 41-50). Ward et al. teach hapten labels well known in the art at the time the claimed invention and they teach specifically teach the claimed hapten labels comprising biotin and imino-biotin wherein biotin and imino-biotin are the preferred labels (Column 6, lines 26-39). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the preferred biotin or imino-biotin hapten label to the hapten label of Nikiforov et al. based on available reagents for the obvious benefit of economy i.e. one skilled in the art having biotin readily available would have been motivated to use the available biotin as a hapten in the method of Nikiforov et al. based on the teaching of Ward et al. wherein biotin is a preferred hapten for the obvious benefit of using available reagents to thereby save the cost of purchasing additional reagents. Likewise, one skilled in the art having imino-biotin readily available would have been motivated to use the available imino-biotin as a hapten in the method of Nikiforov et al. based on the teaching of Ward et al. wherein imino-biotin is a preferred hapten for the obvious benefit of using available reagents to thereby save the cost of purchasing additional reagents.

Applicant further argues that the prior art makes no suggestion to modify or combine their teachings to reach the instant invention. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Lyamichev et al. teach a method similar to those of Nikiforov et al. and Walt et al. wherein the first target domain comprises an overlap domain wherein a first and second probe hybridize respectively to a first and second domain and wherein a cleavage structure is formed if the second probe is complementary to a detection position (page 292, right column and Fig. 2). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the nucleotide detection of Nikiforov et al. with the hybridization and cleavage of Lyamichev et al. for the expected benefit of quantitative detection of a nucleotide and for the additional benefit of economy of time and

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labor by eliminating the amplification and primer extension steps as specifically taught by Lyamichev et al. (page 292, right column second paragraph). The skilled practitioner in the art would have been further motivated to modify the microspheres of Nikiforov et al. with the microspheres on a surface as specifically taught by Walt et al. for the detecting and analyzing a numerous sequences rapidly and automatically using commercially available software as taught by Walt et al. (Column 4, lines 20-28).

Prior Art

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

a. Akhavan-Tafti (U.S. Patent No. 6,013,456, filed 5 February 1999) teaches a method comprising: providing a hybridization complex comprising: a first target sequence comprising: a first nucleotide at a detection position; and a first label specific to said first nucleotide at said detection position; a capture probe attached to a microsphere; and detecting said label to identify said first label to identify said first nucleotide at said detection position (Column 11, lines 63-65 and Column 12, lines 20-54).

b. Weisburg et al. (U.S. Patent No. 6,110,678, filed 1 May 1998) teach a method comprising: providing a hybridization complex comprising: a first target sequence comprising: a first nucleotide at a detection position; and a first label specific to said first nucleotide at said detection position; a capture probe attached to a microsphere on a surface of a substrate; and detecting said label to identify said first label to identify said first nucleotide at said detection position (Column 11, lines 26-57) wherein said microsphere is magnetically held on a surface of a substrate (Column 14, lines 64-67).

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8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


Conclusion


9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


BJ Forman, Ph.D.
May 1, 2001


BJ Forman